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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,211	04/26/2002	Matthias Rudolf Dorsch	047763-5018	4511

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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/018,211	DORSCH ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *402* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed June 16, 2003. Currently, claims 1-17 are pending. Claims 1-9 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group II, Claims 10-17 in the paper filed June 16, 2003 is acknowledged.

Priority

3. This application is a 371 of PCT/AU00/00689, June 19, 2000. The application also claims benefit to PQ 1056, filed June 18, 1999.

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

It is noted that Table 1 does not contain sequence identifiers for all of the sequences provided. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 10-17 are indefinite because it is unclear as to whether the claims are intended to be limited to methods of detecting the presence of viable cells of *Giardia lamblia* or methods of detecting hybridization of the probe and *Giardia lamblia* nucleotides. The claims are drawn to detecting the presence of viable cells of *Giardia lamblia* however, the final step is one of detecting hybridization of the probe and *Giardia lamblia* nucleotides. Accordingly, it is unclear as to whether the claimed method is one for detecting the presence of viable cells of *Giardia lamblia* or detecting hybridization of the probe and *Giardia lamblia* nucleotides.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 10-11, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Shah et al (US Pat. 5,558,989, September 24, 1996).

Shah et al. (herein referred to as Shah) teaches a method for selectively detecting *Giardia lamblia* in a sample using at least one probe that hybridizes to the rRNA but does not hybridize to other organisms (abstract). Shah teaches that the invention is useful because it increases specificity for detecting *Giardia lamblia* in a sample and faster results because the test does not require isolation of *Giardia lamblia* from the sample prior to testing (col. 1, lines 60-65). The method of Shah comprises 1) obtaining a sample to be analyzed, 2) treating the sample to render the nucleic acids present available for hybridization with complementary nucleotide sequences, 3) combining the sample with at least one selected nucleic acid probe and 4) detecting hybridization of the selected nucleic acid probes present in a treated sample (col. 2, lines 25-35)(limitations of Claim 10). Claim 10 is drawn to a comprising method, thus, the claim encompasses additional steps including lysing the cells to detecting hybridization of the probe and *Giardia lamblia* nucleotides.

Shah teaches that nucleic acid probes which are specific for rRNA of *Giardia lamblia* used either individually or in combination. Shah specifically identifies several probes including 1672 which comprises SEQ ID NO: 3 of the instant application (limitations of Claim 11). Shah provides, in Figure 1A and 1B an alignment of *G. lamblia* and *E. coli* with probes. For example, SEQ ID NO: 2 is located in P1449, SEQ ID NO: 3 is located within P1672, SEQ ID NO: 4 is located within and immediately upstream of P1450; SEQ ID NO: 5 is located within and immediately downstream of P1450 and SEQ

ID NO: 6 is located at the 3' end of the sequences depicted. Shah specifically designs probes that utilize the nucleotide sequence differences between *Giardia lamblia* and other parasites and bacteria for distinguishing the organisms. Therefore, as required by the claims the probe has (comprises) SEQ ID NO: 2 or 3. Moreover, the probe comprises a part of the sequence above having at least 10 bases which hybridizes to unique rDNA/rRNA sequences, namely SEQ ID NO: 4, 5 and 6. As seen in Table 1, Shah performs dot blots which specifically detect only *Giardia* but fail to detect other organisms, such as *E. coli, Bacillus, Candida, Staphylococcus*, etc (col. 10-12). Shah teaches that probe sets which include two or more selected nucleic acid probes, each which hybridize to a different region may be used to provide greater sensitivity and specificity (col. 4, lines 46-53). Shah teaches that any sample in which *Giardia lamblia* is suspected may be used, including clinical samples and environmental samples such as water (col. 2, lines 39-48)(limitations of Claim 17). Shah teaches that labeled detector probes may be used (col. 3, lines 47-50).

Therefore, since Shah teaches every limitation of the instant claims, Shah anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah et al (US Pat. 5,558,989, September 24, 1996) in view of Sogin et al. (Genbank Accession Number M54878, April 1993).

Shah et al. (herein referred to as Shah) teaches a method for selectively detecting *Giardia lamblia* in a sample using at least one probe that hybridizes to the rRNA but does not hybridize to other organisms (abstract). Shah teaches that the invention is useful because it increases specificity for detecting *Giardia lamblia* in a sample and faster results because the test does not require isolation of *Giardia lamblia* from the sample prior to testing (col. 1, lines 60-65). The method of Shah comprises 1) obtaining a sample to be analyzed, 2) treating the sample to render the nucleic acids present available for hybridization with complementary nucleotide sequences, 3) combining the sample with at least one selected nucleic acid probe and 4) detecting hybridization of the selected nucleic acid probes present in a treated sample (col. 2,

lines 25-35)(limitations of Claim 10). Claim 10 is drawn to a comprising method, thus, the claim encompasses additional steps including lysing the cells to detecting hybridization of the probe and *Giardia lamblia* nucleotides. Shah teaches that nucleic acid probes which are specific for rRNA of *Giardia lamblia* used either individually or in combination. Shah specifically identifies several probes including 1672 which comprises SEQ ID NO: 3 of the instant application (limitations of Claim 11). Shah provides, in Figure 1A and 1B an alignment of *G. lamblia* and *E. coli* with probes. For example, SEQ ID NO: 2 is located in P1449, SEQ ID NO: 3 is located within P1672, SEQ ID NO: 4 is located within and immediately upstream of P1450; SEQ ID NO: 5 is located within and immediately downstream of P1450 and SEQ ID NO: 6 is located at the 3' end of the sequences depicted. Shah specifically designs probes that utilize the nucleotide sequence differences between *Giardia lamblia* and other parasites and bacteria for distinguishing the organisms. As seen in Table 1, Shah performs dot blots which specifically detect only Giardia but fail to detect other organisms, such as *E. coli, Bacillus, Candida, Staphylococcus*, etc (col. 10-12). Shah teaches that probe sets which include two or more selected nucleic acid probes, each which hybridize to a different region may be used to provide greater sensitivity and specificity (col. 4, lines 46-53). Shah teaches that any sample in which *Giardia lamblia* is suspected may be used, including clinical samples and environmental samples such as water (col. 2, lines 39-48)(limitations of Claim 17). Shah teaches that labeled detector probes may be used (col. 3, lines 47-50).

Shah does not specifically teach a nucleic acid comprising SEQ ID NO: 4 and SEQ ID NO: 6.

However, Sogin teaches the full length rRNA from *Giardia lamblia* which comprises SEQ ID NO: 4 and 6.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have generated equivalent probes for detecting *Giardia lamblia*, as taught by Shah in view of the full 18S rRNA sequence of Sogin so as to obtain the claimed invention as a whole. The teachings of Shah as to the ability to design nucleic acids which distinguish between *Giardia lamblia* and other microorganisms. Although Shah does not explicitly teaches the use of instantly claimed SEQ ID NO: 4, and 6 as specific probes, absent any unexpected results with the instantly claimed SEQ ID NO:s, the instantly claimed specific probes are considered to be functionally equivalent to those of Shah because there is substantial overlap between the instantly claimed primers and those of Shah and further because Shah teaches the usefulness of the 18S rRNA region for detecting *Giardia lamblia* and also teaches that one of skill in the art can modify the disclosed specific probes based on factors such as probe length, melting temperature, and sequence content. Since the claimed oligonucleotides simply represent functional equivalents of the probes disclosed by Shah, the ordinary skilled artisan would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Additionally, at the time the invention was made, the sequence of the 18S rRNA of *Giardia lamblia* was known (as

seen in Sogin) and it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made and within the skill of the art to obtain the instantly claimed oligonucleotides following the teachings of Shah as to the identification of sequences that are specific and thus useful for the identification of *Giardia lamblia* hybridization.

Considering the alignment provided by Shah, it is clear that SEQ ID NO: 4 and 6 are located in regions which contain extreme differences in sequence between *Giardia lamblia* and *E. coli* or in a region where there is no corresponding sequence. SEQ ID NO: 4 is located at the first 9 nucleotides of Figure 1B. SEQ ID NO: 6 is locates at the last 11 nucleotides of Figure 1B. Thus, each of these regions would be ideal regions to target within the 18S rRNA. Therefore, designing probes to each of these regions would have been obvious given the teachings of Shah and Sorgin. Further, the teachings of Shah indicate that the state of the art at the time the invention was made would have led one of ordinary skill in the art to the claimed specific probes because Shah teaches the usefulness of the 18S rRNA region of the *Giardia lamblia* for specific probes and further teaches methods in which the probes may be modified. Therefore, in view of the disclosure of Shah, the use of a specific probe comprising SEQ ID NO: 4 or 6 as specific probes would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

9. Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah et al (US Pat. 5,558,989, September 24, 1996) in view of Williams (WO 96-34978, November 1996).

Shah et al. (herein referred to as Shah) teaches a method for selectively detecting *Giardia lamblia* in a sample using at least one probe that hybridizes to the rRNA but does not hybridize to other organisms (abstract). Shah teaches that the invention is useful because it increases specificity for detecting *Giardia lamblia* in a sample and faster results because the test does not require isolation of *Giardia lamblia* from the sample prior to testing (col. 1, lines 60-65). The method of Shah comprises 1) obtaining a sample to be analyzed, 2) treating the sample to render the nucleic acids present available for hybridization with complementary nucleotide sequences, 3) combining the sample with at least one selected nucleic acid probe and 4) detecting hybridization of the selected nucleic acid probes present in a treated sample (col. 2, lines 25-35)(limitations of Claim 10). Shah teaches that nucleic acid probes which are specific for rRNA of *Giardia lamblia* used either individually or in combination. Shah specifically identifies several probes including 1672 which comprises SEQ ID NO: 3 of the instant application (limitations of Claim 11). Shah provides, in Figure 1A and 1B an alignment of *G. lamblia* and *E. coli* with probes. For example, SEQ ID NO: 2 is located in P1449, SEQ ID NO: 3 is located within P1672, SEQ ID NO: 4 is located within and immediately upstream of P1450; SEQ ID NO: 5 is located within and immediately downstream of P1450 and SEQ ID NO: 6 is located at the 3' end of the sequences depicted. Shah specifically designs probes that utilize the nucleotide sequence

differences between *Giardia lamblia* and other parasites and bacteria for distinguishing the organisms. As seen in Table 1, Shah performs dot blots which specifically detect only Giardia but fail to detect other organisms, such as *E. coli, Bacillus, Candida, Staphylococcus*, etc (col. 10-12). Shah teaches that probe sets which include two or more selected nucleic acid probes, each which hybridize to a different region may be used to provide greater sensitivity and specificity (col. 4, lines 46-53). Shah teaches that any sample in which *Giardia lamblia* is suspected may be used, including clinical samples and environmental samples such as water (col. 2, lines 39-48)(limitations of Claim 17). Shah teaches that labeled detector probes may be used (col. 3, lines 47-50).

Shah does not specifically teach using FISH and two different oligonucleotide probes differentially labeled to detect *Giardia lamblia*.

Williams et al. (herein referred to as Williams) teaches a method for the detection of viable C. parvum oocysts (cells). Williams teaches that FISH is a method which microorganisms can be specifically labeled which is reliant upon the identification of a specific sequence of nucleic acid within the target organism. Probes targeting a specific nucleic acid sequence are synthesized and labeled with a fluorochrome, the cell is permeabilised and allowed to hybridize with the target sequence resulting in specific labeling of the target cell. Williams teaches using fluorescence in situ hybridization (FISH) in which the oligonucleotide probe is labeled with fluorochrome and the resulting cell is detected by flow cytometry (limitations of Claims 14 and 16). Williams teaches that using different fluorochromes is preferred (limitations of Claim 15). Williams specifically teaches aligning 18S rRNA sequences and aligning them to determine

regions which discriminate the species from other species. Williams teaches fixing cells, hybridizing the cells with probes, and performing flow cytometry. Williams teaches that rRNA are ideal targets for fluorescently labeled nucleic acid probes because of the high sensitivity that can be achieved since the target molecules are present in very high numbers; a denaturation step is not required during the procedure as the target region is single stranded and rRNA has a short half life and will only be present in a high copy number in viable cells (page 2). The ordinary artisan would have recognized that the method of FISH followed by flow cytometry added benefits over hybridization assays in lysed cells, as taught by Shah. The method of Williams also allows the detection of viable versus dead cells, as the probes in dead cells the probes bind to rRNA which deteriorate rapidly and is not present in sufficient copy numbers to be detected (page 11). Moreover, Williams teaches that by using FISH, the samples may be fixed and stored prior to analysis, in contrast to samples which must be analyzed immediately (page 12).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified the nucleic acid detecting method of Shah with the in situ method of Williams. The methods of Williams allows detection of viable cells within a sample without lysing the cells or otherwise destroying the cells, allows discriminating between viable and dead cells, allows fixing cells for later analysis and is more sensitive because rRNA is detected before the rRNA deteriorates. The ordinary artisan would have been motivated to have substituted an *in situ* assay for the *in vitro* method of Shah for the expected benefits explicitly provided by Williams. Thus,

the ordinary artisan would have been motivated to have performed FISH analysis followed by flow cytometry as specifically taught by Williams.

Conclusion

10. No claims allowable over the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
September 5, 2003